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Psychosocial adversity in infancy and mortality rates in childhood and adolescence: A birth cohort study of 1.5 million individuals

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Abstract

Background: Childhood and adolescent mortality accounts for a substantial proportion of years lost prematurely. The ability to reduce childhood and adolescent mortality relies on knowing the characteristics of those at elevated risk of dying young. We therefore aimed to identify such characteristics with the main hypothesis being that psychosocial adversity in infancy be linked to increased mortality rates in childhood and adolescence.

Methods: We conducted a cohort study involving all 1,549,581 children born in Denmark between January 1st 1981 and December 31st 2010 to Danish born parents. For each child, we extracted values from national registers regarding Rutter's indicators of adversity (RIA) in infancy (low social class, parents not cohabiting, large family size, paternal criminality, maternal mental disorder, and placement in out-of-home care). Follow-up began on the cohort members' first birthday. The association between RIA-scores and death was estimated via Cox regression.

Results: During follow-up (18,874,589 person-years), 2081 boys and 1420 girls died prior to or on their 18th birthday. The hazard ratios for death were 2.3 (95%CI: 1.9-2.9) and 2.1 (95%CI: 1.6-2.7) for boys and girls with RIA-scores of 3-6, compared to boys and girls with RIA-scores of 0. These associations were driven by causes of death with known links to psychosocial adversity.

Conclusions: While absolute mortality rates were low, infants with RIA-scores of 3-6 were approximately twice as likely to die prematurely compared to infants with RIA-scores of 0. Initiatives to reduce childhood and adolescent mortality rates among individuals exposed to early psychosocial adversity should be prioritized further.

Introduction

Childhood and adolescent mortality accounts for a substantial proportion of the years lost prematurely.[1,2] Whenever a child or adolescent dies it is a tragedy for the immediate surroundings, but it also represents a substantial loss of potential for the society the deceased individual belonged to. While infant mortality rates have decreased dramatically over the past decades,[1-3] post infancy childhood and adolescent mortality rates have not decreased to the same extent.[1,2] Thus, there is a substantial room for improvement of life expectancy by reducing post infancy childhood and adolescent mortality rates.

The ability to reduce childhood and adolescent mortality relies on knowing the characteristics of those at elevated risk of dying young as well as the causes of which they die. Prior studies have established that there is an association between psychosocial adversity and mortality in adulthood.[4,5] However, whether there is an association between very early psychosocial adversity and mortality in childhood and adolescence has received little attention.[6] If such an association is present it could facilitate targeting of interventions to reduce the morbidity and mortality of young people in the future.[7,8]

Based on our recent findings i) that Rutter's indicators of adversity (RIA: low social class, parents not cohabiting (original Rutter definition: severe marital discord), large family size, paternal criminality, maternal mental disorder, and placement in foster care)[9] assessed in infancy is associated with later development of attention deficit hyperactivity disorder (ADHD)[10] and ii) that ADHD is associated with premature mortality,[11] it seems likely that RIA assessed in infancy would be associated with childhood and adolescent mortality. Therefore, we conducted a study in which the following three hypotheses were tested:

1) RIA assessed in infancy are positively associated with childhood and adolescent mortality.

2) The association between RIA and childhood and adolescent mortality is not fully accounted for by mental disorders in the children and adolescents.

3) The association between RIA and childhood and adolescent mortality is cause-specific and primarily driven by causes linked to psychosocial adversity such as congenital malformations,[12] infections,[13] endocrine diseases and deficiencies,[14,15] traffic accidents and other unnatural causes of death.[16,17]

Methods

Design

We conducted a population-based cohort study. Data from multiple registers was linked via the unique personal registration numbers that are assigned to all Danes at the time of birth.[10,18]

Cohort and follow-up

The cohort was defined via the Danish Civil Registration System[18] as all children born in Denmark between January 1st 1981 and December 31st 2010 that were living in Denmark on their 1st birthday. Only children of parents who were known to be born in Denmark were included in the cohort. The parents of the cohort members were also identified through the Danish Civil Registration System. Follow-up of the cohort members commenced on their 1st birthday and ended with the first of the following events: death, emigration, 18th birthday or December 31st 2011.[10]

Primary outcome (death)

The date of death was extracted from the Danish Civil Registration System[18] and the cause of death was extracted from the Danish Cause of Death Register,[19] where all deaths are registered with an 8th International Classification of Diseases (ICD-8)[20] code (until December 31st 1993) or an 10th International Classification of Diseases (ICD-10)[21] code (from January 1st 1994 and onwards).[10]

Definition of Rutter's indicators of adversity (RIA)

RIA were defined based on register data in accordance with our recent study on ADHD.[10] In brief:

Low social class: Low social class of the cohort member's parents was defined (dictotomously) as both the father and the mother being classified as "low" on one or more of the following variables: education, occupation or income. Low education was defined as only having completed (or not having completed)

compulsory schooling[22] on October 1st in the cohort member's year of birth. Low occupation was defined as receiving disability pension (typically a permanent pension due to physical or mental illness) on November 1st in the cohort member's year of birth.[23] Low income was defined as having a gross income in the lowest fifth of the population-based income distribution (sex- and calendar year specific) in the cohort member's year of birth.[24]

Parents not cohabiting: Parents not cohabiting (used as proxy for severe marital discord[9]) was defined (dichotomously) based on whether the custodial parents lived at the same address as the cohort member on January 1st in the year following the cohort member's year of birth.[10,25]

Large family size: Large family size was defined (dichotomously) as a household with four (including the cohort member) or more residing children (<18 years of age) on January 1st in the year after the cohort member's year of birth.[10,26]

Paternal criminality: Paternal criminality was defined (dichotomously) based on whether the father of the cohort member had ever received a suspended or custodial sentence for an offence under the principal Danish criminal acts (e.g., theft, fraud, extortion, robbery, violence, murder, sexual crime or arson), sections of the traffic act dealing with impaired driving or the special legislation regarding weapons and drugs.[27] Information on all convictions between January 1st 1980 and the cohort member's 1st birthday was considered.

Maternal mental disorder: Maternal mental disorder was defined (dichotomously) based on whether the mother of the cohort member had been registered with a diagnosis of a mental disorder in the Danish Psychiatric Central Research Register (DPCRR)[28] in the period between January 1st 1969 and the cohort member's first birthday.

Placement in out-of-home care: Placement in out-of-home care was defined (dichotomously) based on whether the cohort member had ever been placed outside home (foster care/orphanage/institution) either without or with the parents' consent prior to his or her first birthday.[29]

Statistical analyses

Absolute mortality risks and hazard rates where estimated using Kaplan-Meier and Epanechnikov kernel estimators.[30] We also calculated the difference in mortality hazards (with corresponding 95% confidence bands) for cohort members with RIA-scores of 1, 2, or 3-6 compared to those with a RIA-score of 0 at ages 5, 10, and 15 years, respectively, stratified by sex.

The association between RIA and mortality was tested by means of Cox regression using age as the underlying time-axis via the "stcox" command in Stata (version 13). The strength of the associations was described by hazard ratios with 95% confidence bands. These analyses were adjusted for calendar year (1 year strata) and stratified by sex. The Stata code for the analyses is available in eAppendix1.

To determine if potential associations between elevated RIA-scores and mortality were driven by single RIA, "leave-one-out" analyses were conducted in which each of the individual RIA, in turn, were excluded from the RIA-score in the Cox regression analyses investigating the association between RIA-scores and mortality. Relatedly, in order to investigate if any of the RIA had disproportionally small/large effects on mortality, we conducted add-one-in analyses, in which we adjusted the association between the RIA-score and mortality for each of the RIA's one by one in the Cox regression. Also, we assessed the pair-wise association between the individual RIA by means of Pearson correlation.[10]

The cause specific mortality across RIA-scores assessed in infancy was also calculated by means of Cox regression using age as the underlying time-axis via the "stcox" command in Stata (version 13). The strength of the associations was described by hazard ratios with 95% confidence bands. These analyses

were also adjusted for calendar year (1 year strata) and stratified by sex. In addition to the causes of death we hypothesized would be associated with psychosocial adversity, namely congenital malformations, infections, endocrine diseases and deficiencies, traffic accidents and other external/unnatural causes of death, the following categories of causes were considered (as "negative control" outcomes): cancer, diseases of the nervous system or sensory organs, and other causes of death. The ICD-8 and ICD-10 codes used to define these categories of causes are available in eAppendix2.

Based on our findings in ADHD,[11] we tested whether any associations between RIA and mortality was accounted for by mental disorder by repeating the Cox regression analyses described above,[31] while adding adjustment for the psychiatric history of the cohort members (time dependent based on the date of diagnosis in the DPCRR) with the following levels: no mental disorder, any mental disorder apart from ADHD, and ADHD (defined by an ICD-8 diagnosis of 308.01 or an ICD-10 diagnosis of F90.x or F98.8).[11]

Sensitivity analyses

Four sensitivity analyses were performed as follows: **I)** Since the definition of parents not cohabiting was defined as whether the custodial parents were living at the same address as the subject or not on January 1st in the year following the subject's year of birth, a cohort member's status on this variable could be affected by his/her status on the placement in out-of-home care variable, i.e., some with a positive placement in out-of-home care status were potentially assigned with a positive parents not cohabiting status even though their custodial parents lived together, but on a different address than the cohort member. To test whether this potential misclassification affected the findings of the main analyses, we repeated the relevant analyses after reclassifying the parents not cohabiting status of the 3299 cohort members with positive status on both placement in out-of-home care and parents not cohabiting, such that they only had positive status on placement in out-of-home care. **II)** Since RIA is somewhat gender biased (only considering maternal mental disorders and paternal criminality), we repeated the analyses of the association between RIA and mortality after adding paternal mental disorder (i.e., the resulting variable

covered parental mental disorder) and maternal criminality (i.e. the resulting variable covered parental criminality). The definitions of paternal mental disorder and maternal criminality were analogue to those for the other sex - as described above. **III)** To test whether RIA status in infancy increases mortality risk in the same fashion throughout childhood and adolescence, we conducted age-stratified Cox regression analyses (age <6, age 6-10, and age >10) of the association between RIA and mortality. This analysis included a test of interaction between age group and RIA status for both the individual RIA as well as for the overall RIA-score. **IV)** While the primary focus of this study was the association between psychosocial adversity in infancy and mortality in the age from 1-17 years, the association between psychosocial adversity and mortality in infancy is also of considerable interest. Therefore, we assessed the association between the four components of RIA that could be operationalized before birth of the cohort member (low social class, large family size, paternal criminality and maternal mental disorder) and mortality in infancy. See eAppendix2 for a detailed description of the infant mortality analysis.

Ethics

The use of data from the registers was approved by the Danish Data Protection Agency, the Danish National Board of Health and Statistics Denmark.

Results

A total of 1,887,191 children were born in Denmark between January 1st 1981 and December 31st 2010. For 329,263 of these children both parents (n=3755) or the father (n=17,399) or the mother (n=444) were unregistered, and/or both parents (n=135,577) or the father (n=87,171) or the mother (n=84,917) were either not born in Denmark or their country of birth was unknown. Of the remaining 1,557,928 children of parents born in Denmark, 8347 either died, emigrated, were lost to follow-up before their first birthday or were born on December 31st 2010 and did therefore not contribute with time at risk. Thus, our final cohort consisted of 1,549,581 children (795,130 males and 754,451 females), who were followed from their 1-year birthday yielding a total of 18,874,589 person-years of observation.

The prevalence of the six RIA in infancy were as follows in the final cohort: paternal criminality: 9.3% in males and 9.4% in females, parents not cohabiting: 10.8% in males and 10.8% in females, low social class: 12.3% in males and 12.3% in females, maternal mental disorder: 4.0% in males and 4.0% in females, large family size: 3.3% in males and 3.4% in females, placement in out-of-home care: 0.3% in males and 0.3% in females.

During follow-up, 2081 males and 1420 females died corresponding to mortality rates of 2.2 (95%CI: 2.1-2.2) and 1.6 (95%CI: 1.5-1.6) per 10,000 person-years respectively. Figure 1 shows the expected "bathtub" shaped mortality hazard rates that decrease across birth decades (1980-1989, 1990-1999 and 2000-2013) and that are generally higher in males compared to females.

Figure 1 approximately here

Table 1 shows mortality rates and mortality hazard ratios for each of the six RIA, as well as for the summed RIA, stratified on males and females. For males, the mortality rates per 10,000 person-years for the six RIA ranged from 2.6 (95%CI: 2.1-3.2) for large family size to 9.7 (95%CI: 6.7-14.1) for placement in out-of-home

care for males. The corresponding hazard ratios ranged from 1.2 (95%CI: 1.0-1.5) to 4.3 (95%CI: 3.0-6.3). For females, the mortality rates per 10,000 person-years for the six RIA ranged from 1.8 (95%CI: 1.4-2.4) for maternal mental disorder to 9.6 (95%CI: 6.4-14.3) for placement in out-of-home care. The corresponding hazard ratios ranged from 1.2 (95%CI: 0.9-1.6) to 5.6 (95%CI: 3.8-8.4). Notably, the hazard ratios were virtually unchanged by adjustment for the psychiatric history of the cohort members (see Table 1).

Table 1 also shows that there was a marked dose-response relationship between the summed RIA-score and the risk of early death for both males and females. Specifically, the hazard ratios for death were 2.3 (1.9-2.9) and 2.1 (1.6-2.7) respectively, for males and females with RIA-scores of 3-6, compared to males and females with RIA-scores of 0. The dose-response relationship between the RIA-score and the risk of death is visualized by the Kaplan-Meier plots shown in Figure 2 and is also evident in the mortality hazard differences reported in eTable1 (see eAppendix2).

Table 1 and Figure 2 approximately here

The results of the leave-one-out analysis, which indicate that the relationship (dose-response) between the RIA-score and mortality rates is maintained irrespective of which RIA is excluded from the score, are shown in eTable2 (see eAppendix2). The results of the add-one-in analysis, which demonstrate that placement in out of home care has a disproportionally strong association with early death compared to the other RIA, are outlined in eTable3 (see eAppendix2).

The Pearson correlation coefficients representing the pair-wise association between the individual RIA are shown in Table 2. The correlation coefficients ranged from -0.00 parents not cohabiting and large family size to 0.21 for paternal criminality and low social class.

Table 2 approximately here

Table 3 shows the hazard ratios for cause specific mortality across total RIA-scores assessed in infancy. There was dose-response relationship between the summed RIA-score and the risk of early death due to the following causes for both males and females: traffic accidents, other external causes of death, and infectious diseases. Again, the hazard ratios were virtually unchanged by adjustment for the psychiatric history of the cohort members.

Table 3 approximately here

The results of the sensitivity analyses are reported in eAppendix2. The results of the analyses testing whether potential misclassifications of parents not cohabiting had any effect on the associations between RIA assessed in infancy and early mortality are consistent with those of the corresponding primary analyses (see eTables4-7 compared to Table 1, Table 3, eTable2 and eTable3). Thus, any misclassifications of parents not cohabiting status appear to have had only minor effect. Similarly, the results for the analyses, which considered parental mental disorder and parental criminality are consistent with those from the analyses, which considered only maternal mental disorder and paternal criminality (see eTables8-11 compared to Table 1, Table 3, eTable2 and eTable3). Also, the results of the age-stratified Cox regression analyses (age <6, age 6-10, and age >10) showed that the association between RIA assessed in infancy and early mortality was quite consistent across these age-strata, with some exceptions in males (see eTable12). Notably, the positive dose-response relationship between the RIA-score assessed in infancy and mortality was found in all three age-groups for both females and males. Finally, the sensitivity analysis, which assessed the association between RIA-scores and infant mortality showed the same dose-reponse relationship as for the association between RIA-scores and mortality in post-infancy childhood or adolescence (see eTable13 compared to Table 1).

Discussion

In this study of 1,549,581 Danish children followed for a total of 18,874,589 person-years we found a low overall mortality rate, but also a clear dose-response relationship between the level of psychosocial adversity in infancy (as operationalized by Rutter's indicators of adversity (RIA)) and mortality rates in childhood and adolescence in both males and females. Sensitivity analyses showed that elevated levels of psychosocial adversity were also associated with infant mortality.

As hypothesized, the positive association between psychosocial adversity and mortality rates in childhood and adolescence were primarily driven by causes of death with known links to psychosocial adversity, namely traffic accidents, other external causes of death (covering suicide, homicide, and non-traffic accidents (accidental drowning, poisoning, falls, fires, suffocation, strangulation, aspiration, choking etc.) and infectious diseases. We expected to see similar positive associations with deaths due to congenital malformations and endocrine diseases and deficiencies, but here the picture was less clear, possibly due to a combination of weaker associations (if any) with the very low number of deaths for the causes among individuals with high levels of psychosocial adversity (see Table 3). Also, a large proportion of deaths due to congenital malformations are likely to have occurred already in infancy and are therefore not included in this study of post-infancy mortality. Indeed, the results of our sensitivity analysis of the association between RIA-scores and infant mortality due to congenital malformations (see eTable 14) were indicative of a dose-response relationship.

Notably, the association between psychosocial adversity and early mortality rates was largely unaffected by adjusting for the history of mental disorder of the cohort members. Thus, it appears that a potential causal effect between psychosocial adversity and early death is unlikely to be mediated by mental disorders, such as ADHD.[11]

Although all six RIA seem to contribute to increased risk of early death, the add-one-in analysis (see eTable3) shows that placement in out of home care is associated with a disproportionally large risk of early death compared to the other RIA. As indicated by the very low prevalence of this intervention in infancy (affecting 0.3% of the cohort members), placement in out of home care is typically only used in cases, where a range of less "intrusive" in-home initiatives (counseling, family therapy or specialized daycare) have been tried and failed. The decision to place a child in out of home care is based on a very thorough multidisciplinary assessment of the child's health, behavior, development, family, schooling, spare-time activities, friendships, etc. coordinated by the social authorities.[29] The exact reason underlying the decision to place a child in out of home care is unfortunately not available in the Danish registers – and will often be highly complex/multifactorial.[29] There is however some information available on the context in which out of home placements occur in Denmark. Specifically, in a Danish register-based study focusing on the transition from in-home support (initiated prior to the age of three) to placement in out of home care, the following factors were positively associated with transition to placement in out of home care within two years: child diagnosed with a mental illness, low birth weight of the child, child having a sibling in care, single motherhood, either parent diagnosed with a mental illness, or father being unemployed.[32] Relatedly, another Danish register-based study showed that among children who were placed in out of home care for the first time prior to the age of three, only 39% were reunified with their families within five years.[29] Taken together, these prior findings indicate that very young children placed in out of home care are likely to have been exposed to such significant adversity in the environment they were removed from, that they are both physically and mentally vulnerable, which translates to increased risk of early death in the present study.

Due to the observational nature of this study, we can only speculate with regard to the mechanisms underlying the positive association between RIA assessed in infancy and early mortality. Intuitively, due to the definition of the individual RIA, both genetic and environmental factors are likely to be in play.

Collectively - and most likely in interaction - these factors will contribute to increased risk of reduced physical and mental health, where premature death is the most extreme of potential outcomes.

Our finding that infants with RIA-scores of 3-6 are approximately twice as likely to die prematurely compared to infants with RIA-scores of 0 is compatible with the growing body of literature showing that adverse early environments are strong predictors of the lacking development of cognitive and non-cognitive abilities,[33-35] that account for a substantial fraction of social and economic problems in modern societies.[36] These observations from prior studies have led to the formation of childhood programs aiming at improving the abilities of disadvantaged children.[37] It has been suggested that the payoff of such programs are likely to be particularly pronounced if the intervention is targeted towards children who do not receive sufficient parental care in the very early years, but such children are difficult to identify at that early stage.[38] Based on the findings from the study reported here – and the results of our analogue study of ADHD[10] – we believe that RIA can be used for early (infancy) identification of exposure to psychosocial adversity – and hence to target supportive measures. Furthermore, when looking at the causes of death responsible for the increased mortality in children experiencing early psychosocial adversity, i.e. traffic accidents and other external causes of death and infectious diseases, targeted interventions to prevent accidents[39] and infections[40,41] in these children would also seem to be of relevance.

The key limitation of our study is the use of register-based definitions of RIA. While our definitions of placement in out-of-home care, low social class, paternal criminality, maternal mental disorder and large family size are largely equivalent to those from prior studies of RIA, the operationalization of severe marital discord (where we used “parents not cohabiting” as a proxy) differs substantially from that of other studies. As the available register data does not contain information about the extent and nature of interpersonal conflicts among the parents of the cohort members in this study, we used parents not cohabiting (defined as whether both custodial parents were living at the same address as the cohort member or not) as a proxy for severe marital discord. At present, we are unable to test empirically whether this definition covers the

same construct as severe marital discord defined by Rutter et al.[9] However, based on the results of this study and our analogue study of ADHD,[10] we believe that our operationalization (parents not cohabiting) indeed does tap into some aspect of psychosocial adversity.

Furthermore, there is also a limitation associated with the operationalization of mental disorder among the cohort members in the study. Since the information to define this variable was extracted from diagnostic data in the DPCRR, the variable only captures relatively severe mental health problems, which have led to hospital contact and a subsequent diagnosis. Having information from mental health assessments of all cohort members would have been preferable, but such data is unfortunately not available in the Danish registers. Therefore, the adjustment of the associations between psychosocial adversity and mortality does not take less severe mental health problems into account. However, given that the adjustment for (relatively severe) mental disorder among the cohort members did not change these associations, this limitation seems to be of minor importance.

The register-based approach of this study also has strengths. Most importantly, the fact that our data are derived from registers virtually eliminates the risk of report bias, which is a potentially severe problem in studies of self-report of psychosocial adversity. Furthermore, the use of registers has allowed us to follow a birth cohort of more than 1.5 million individuals over more than 18.8 million person-years, which is instrumental in the study of rare events such as deaths in children and adolescents.

It is important to underline that the results reported in this manuscript are based entirely on children where both parents were born in Denmark. This was done in order to have complete data regarding RIA. However, while we do not have data to support this point of view, we have no reason to believe that the association between RIA and early mortality should be different among children of foreign parents compared to that for children of Danish parents. Relatedly, the reader should keep in mind that Denmark is among the most socially and financially equal welfare states in the world.[42] Therefore, the strength of the

associations between RIA and childhood and adolescent mortality rates observed in this study may not be applicable to countries providing other levels of welfare to its citizens. Given that the possibilities for social support and health care are very good in Denmark, it seems likely that the association between early psychosocial adversity and mortality may be even more pronounced in societies with a less developed welfare system. Also, the fact that only 2% of the cohort members in this study belonged to the high psychosocial adversity category (RIA-score: 3-6) is unlikely to generalize to societies with a less developed welfare system. Thus, both in terms of the prevalence of psychosocial adversity and the strength of the association between psychosocial adversity and mortality, the results of this study probably represent a "best-case scenario". It would therefore be of considerable interest to test the association between RIA and mortality in other societies.

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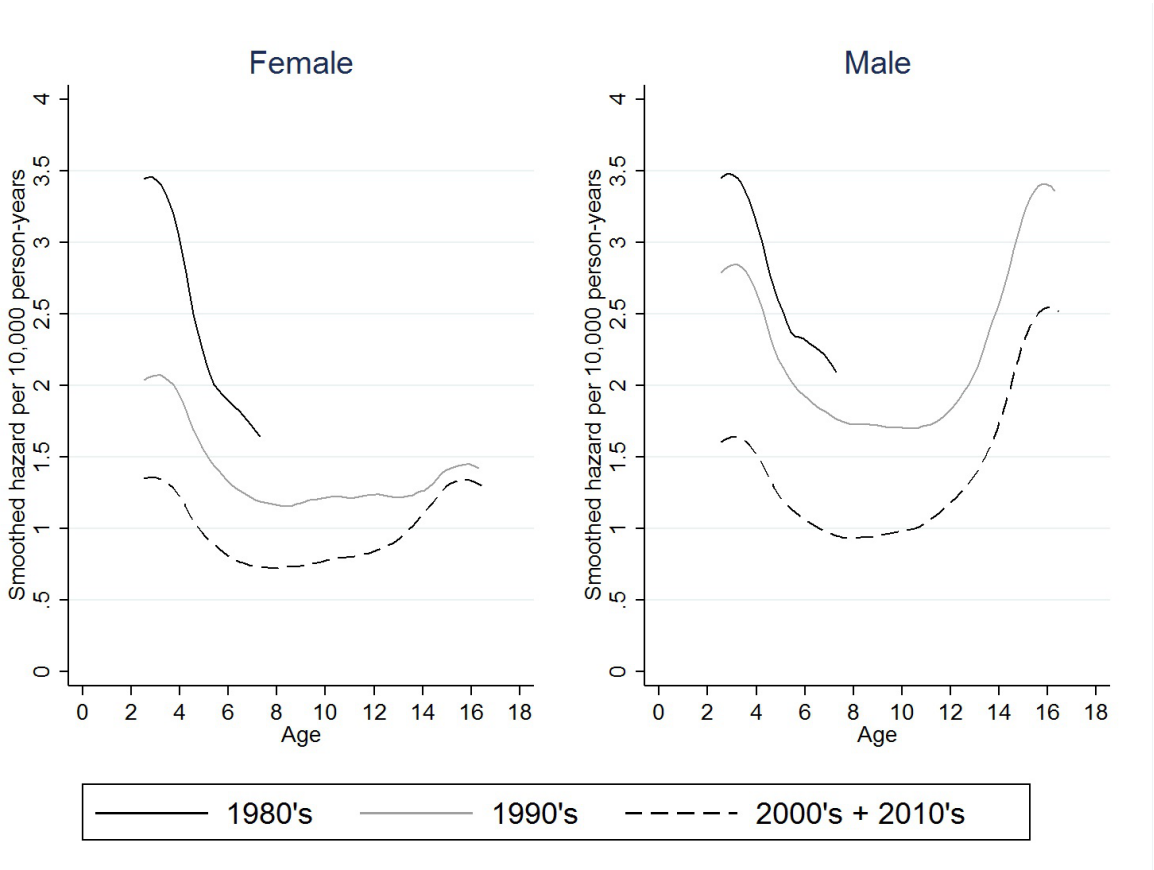
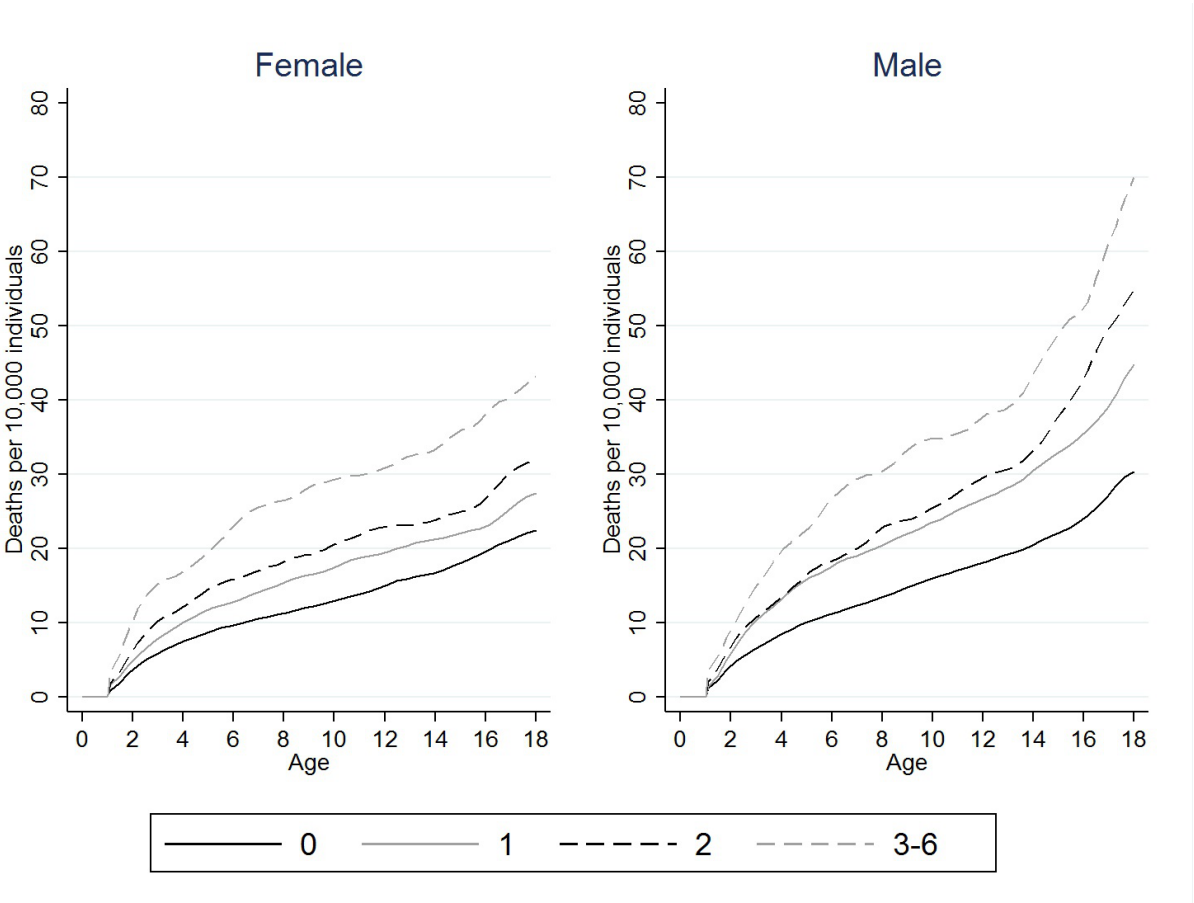
Figure 1. Mortality hazard rates per decade of death



Plots showing the mortality hazard rates stratified by sex and decade for children born in Denmark between 1981 and 2010. The hazard rates were based on an Epanechnikov kernel with an 18 months bandwidth. Therefore the curves are truncated by 1.5 years in both ends (i.e. the smoothed hazard plots start at age 2.5 and end at age 16.5). The curve representing the 1980's ends at 7.5 years, because the eldest children in the cohort (born in January 1981) reach a maximum age of 9 years in 1980. The sample availability at different ages was as follows for females: Age 1, n=754 451 (100%); Age 5, n=655 653 (90%); Age 10, n=530 004 (70%), Age 15, n=400 600 (53%), Age 18, n=144 343 (19%). The corresponding numbers for males: Age 1, n=795 130 (100%); Age 5, n=690 570 (87%); Age 10, n=558 550 (70%), Age 15, n=422 074 (53%), Age 18, n=151 887 (19%).

Figure 2. Risk of death over time stratified by RIA-score.



Kaplan-Meier plots showing the number of deaths per 10 000 individuals among females and males stratified by RIA-score measured in infancy. Due to the relatively low number of cohort members with 3-6 RIA, these curves were smoothened using the Epanechnikov kernel to avoid potential identification of individuals. Note that the follow-up starts at the age of 1 year.

Table 1. Incidence rates and adjusted hazard ratios for mortality for each of Rutter's indicators of adversity (RIA) and across total RIA-scores assessed in infancy

	N deaths	%	N total	%	Rate per 10 000 Person-years (95% CI)	HR (95% CI)*	HR (95% CI)**
FEMALES							
Low social class							
No	1153	81.20	661 297	87.65	1.46 (1.37-1.55)	1.00 (ref)	1.00 (ref)
Yes	266	18.73	92 735	12.29	2.06 (1.83-2.33)	1.32 (1.15-1.51)	1.30 (1.14-1.49)
Parents not cohabiting							
No	1215	85.56	671 315	88.98	1.50 (1.41-1.58)	1.00 (ref)	1.00 (ref)
Yes	203	14.30	81 627	10.82	1.91 (1.66-2.20)	1.28 (1.11-1.49)	1.27 (1.09-1.47)
Large family size							
No	1356	95.49	727 558	96.44	1.53 (1.45-1.61)	1.00 (ref)	1.00 (ref)
Yes	62	4.37	25 384	3.36	2.06 (1.61-2.64)	1.37 (1.06-1.77)	1.37 (1.06-1.77)
Paternal criminality							
No	1268	89.30	683 873	90.65	1.51 (1.42-1.60)	1.00 (ref)	1.00 (ref)
Yes	152	10.70	70 578	9.35	1.86 (1.59-2.19)	1.34 (1.13-1.58)	1.32 (1.11-1.56)
Maternal mental disorder							
No	1371	96.55	724 053	95.97	1.54 (1.46-1.62)	1.00 (ref)	1.00 (ref)
Yes	49	3.45	30 398	4.03	1.84 (1.38-2.44)	1.26 (0.94-1.67)	1.22 (0.91-1.62)
Out-of-home care							
No	1396	98.31	752 389	99.73	1.52 (1.45-1.61)	1.00 (ref)	1.00 (ref)
Yes	24	1.69	2 062	0.27	9.55 (6.40-14.25)	6.07 (4.05-9.08)	5.62 (3.75-8.43)
RIA-score							
0	903	63.59	533 800	70.75	1.39 (1.31-1.50)	1.00 (ref)	1.00 (ref)
1	343	24.15	157 884	20.93	1.74 (1.56-1.92)	1.22 (1.07-1.38)	1.21 (1.07-1.37)
2	118	8.31	46 289	6.14	2.04 (1.70-2.44)	1.45 (1.19-1.75)	1.42 (1.17-1.72)
3-6	56	3.94	16 478	2.18	2.83 (2.19-3.70)	2.08 (1.59-2.73)	2.01 (1.54-2.64)
MALES							
Low social class							
No	1645	79.05	696 789	87.63	1.98 (1.87-2.08)	1.00 (ref)	1.00 (ref)
Yes	434	20.86	97 901	12.31	3.19 (2.89-3.50)	1.49 (1.34-1.66)	1.48 (1.33-1.64)
Parents not cohabiting							
No	1733	83.28	707 300	88.95	2.02 (1.92-2.12)	1.00 (ref)	1.00 (ref)
Yes	345	16.58	86 217	10.84	3.10 (2.79-3.44)	1.52 (1.35-1.70)	1.50 (1.34-1.69)
Large family size							
No	1997	95.96	766 944	96.46	2.14 (2.04-2.23)	1.00 (ref)	1.00 (ref)
Yes	81	3.89	26 573	3.34	2.56 (2.06-3.20)	1.23 (0.99-1.54)	1.23 (0.99-1.54)
Paternal criminality							
No	1814	87.17	721 261	90.71	2.04 (1.96-2.14)	1.00 (ref)	1.00 (ref)
Yes	267	12.83	73 869	9.29	3.14 (2.77-3.54)	1.66 (1.46-1.89)	1.64 (1.44-1.87)
Maternal mental disorder							
No	2008	96.49	763 377	96.01	2.12 (2.04-2.23)	1.00 (ref)	1.00 (ref)
Yes	73	3.51	31 753	3.99	2.62 (2.08-3.31)	1.34 (1.06-1.69)	1.31 (1.04-1.66)
Out-of-home care							
No	2053	98.65	792 857	99.71	2.12 (2.04-2.22)	1.00 (ref)	1.00 (ref)
Yes	28	1.35	2 273	0.29	9.71 (6.70-14.06)	4.33 (2.98-6.29)	4.14 (2.85-6.02)
RIA-score							
0	1235	59.35	562 502	70.74	1.82 (1.72-1.91)	1.00 (ref)	1.00 (ref)
1	567	27.25	166 986	21.00	2.72 (2.50-2.95)	1.46 (1.32-1.61)	1.45 (1.32-1.61)
2	194	9.32	48 398	6.09	3.20 (2.77-3.68)	1.74 (1.49-2.02)	1.72 (1.47-2.00)
3-6	85	4.08	17 244	2.17	4.15 (3.35-5.12)	2.33 (1.87-2.91)	2.28 (1.83-2.84)

"N deaths" refers to the number of deaths in each stratum, while "N total" is the total number of individuals in each stratum. The hazard ratios (HR) are adjusted for calendar year (1 year strata). Information regarding low social class, parents not cohabiting and large family size was unavailable for 0.06%, 0.20%, and 0.20% of the cohort members * Adjusted for age and calendar time. ** Adjusted for age, calendar year and psychiatric history in the cohort members.

Table 2. Pairwise associations between Rutter's Indicators of adversity in infancy

	Low social class	Parents not cohabiting	Large family size	Paternal criminality	Maternal mental disorder	Out-of-home care
Low social class	1					
Parents not cohabiting	0.19	1				
Large family size	0.05	-0.00	1			
Paternal criminality	0.21	0.18	0.02	1		
Maternal mental disorder	0.06	0.08	0.01	0.07	1	
Out-of-home care	0.07	0.11	-0.00	0.06	0.08	1

The pairwise association between the individual Rutter's Indicators of adversity was assessed by means of Pearson correlation. This table contains the resulting Pearson correlation coefficients.

Table 3. Adjusted hazard ratios for cause specific mortality across total RIA-scores assessed in infancy

	Number of deaths	FEMALES HR (95% CI)*	FEMALES HR (95% CI)**	MALES HR (95% CI)*	MALES HR (95% CI)**
Traffic accidents					
RIA-score					
0	361	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	190	1.63 (1.21-2.20)	1.63 (1.20-2.20)	1.65 (1.33-2.05)	1.65 (1.32-2.05)
2	73	2.10 (1.36-3.25)	2.09 (1.35-3.24)	2.27 (1.67-3.09)	2.26 (1.66-3.08)
3-6	25	3.02 (1.63-5.59)	3.00 (1.62-5.57)	2.07 (1.21-3.55)	2.05 (1.20-3.52)
Other external causes of death					
RIA-score					
0	300	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	151	1.66 (1.18-2.33)	1.62 (1.15-2.27)	1.57 (1.24-2.00)	1.56 (1.23-1.98)
2	62	2.49 (1.57-3.96)	2.36 (1.48-3.75)	2.19 (1.56-3.07)	2.13 (1.52-2.99)
3-6	42	4.19 (2.30-7.63)	3.75 (2.05-6.86)	5.02 (3.42-7.37)	4.80 (3.26-7.06)
Infectious diseases#					
RIA-score					
0	131	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	52	0.86 (0.50-1.47)	0.86 (0.50-1.46)	1.64 (1.09-2.46)	1.64 (1.09-2.46)
2	22	1.58 (0.78-3.17)	1.56 (0.78-3.14)	2.12 (1.17-3.83)	2.12 (1.17-3.83)
3-6	14	2.68 (1.08-6.66)	2.63 (1.05-6.54)	4.49 (2.24-9.00)	4.49 (2.24-9.02)
Congenital malformations					
RIA-score					
0	314	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	136	1.33 (0.98-1.81)	1.32 (0.98-1.79)	1.43 (1.09-1.87)	1.42 (1.08-1.86)
2	44	1.56 (0.98-2.50)	1.54 (0.97-2.46)	1.56 (1.02-2.39)	1.53 (1.00-2.35)
3-6	11	1.19 (0.49-2.89)	1.15 (0.47-2.81)	1.20 (0.53-2.70)	1.16 (0.51-2.62)
Endocrine diseases and deficiencies					
RIA-score					
0	79	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	23	0.67 (0.30-1.51)	0.65 (0.29-1.48)	1.17 (0.66-2.08)	1.16 (0.66-2.06)
2	11	1.62 (0.64-4.15)	1.54 (0.60-3.96)	1.52 (0.65-3.56)	1.48 (0.63-3.47)
3-6	4##	-	-	-	-
Cancer					
RIA-score					
0	427	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	148	0.84 (0.62-1.13)	0.83 (0.62-1.13)	1.37 (1.07-1.74)	1.37 (1.08-1.75)
2	32	0.80 (0.47-1.35)	0.80 (0.47-1.35)	0.86 (0.52-1.41)	0.87 (0.53-1.42)
3-6	14	1.44 (0.74-2.81)	1.43 (0.73-2.79)	0.77 (0.32-1.87)	0.78 (0.32-1.90)
Diseases of the nervous system###					
RIA-score					
0	147	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	56	1.36 (0.85-2.20)	1.35 (0.84-2.17)	1.14 (0.76-1.71)	1.13 (0.75-1.69)
2	20	1.36 (0.62-2.99)	1.33 (0.60-2.91)	1.60 (0.90-2.87)	1.56 (0.87-2.80)
3-6	10	4.05 (1.85-8.89)	3.84 (1.74-8.44)	1.12 (0.35-3.54)	1.07 (0.34-3.40)
Other causes of death					
RIA-score					
0	379	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	154	1.22 (0.92-1.61)	1.21 (0.91-1.61)	1.40 (1.09-1.80)	1.39 (1.08-1.79)
2	48	1.01 (0.61-1.69)	1.00 (0.60-1.67)	1.76 (1.21-2.56)	1.72 (1.19-2.50)
3-6	21	0.94 (0.39-2.29)	0.92 (0.38-2.25)	2.62 (1.57-4.36)	2.53 (1.52-4.21)

*Adjusted for age and calendar time. **Adjusted for age, calendar time and psychiatric history in the cohort members, #Infectious diseases (incl. encephalitis / excl. tuberculosis), ##Too few deaths to allow for analysis stratified on sex due to risk of identification of individuals, ###Diseases of the nervous system or sensory organs.